(51) International Patent Classification⁷: C12N 15/63, 5/10, C12Q 1/68, A01K 67/027, A61K 49/00

(21) International Application Number: PCT/AU01/01407

(22) International Filing Date:
1 November 2001 (01.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PR 1161   1 November 2000 (01.11.2000)   AU
PR 4901   10 May 2001 (10.05.2001)   AU

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(54) Title: TRANSGENIC ANIMALS FOR ANALYSING CYP3A4 CYTOCHROME P450 GENE REGULATION

(57) Abstract: The invention relates to the generation of non-human transgenic animals comprising a reporter construct for producing a detectable amount of a reporter molecule operably linked to a transcriptional regulatory nucleic acid molecule from the human CYP3A4 gene located between the initiation of transcription site of the gene and a position located 13,000 nucleotides upstream from the site. The invention also relates to the use of these animals for determining the effect of a compound, particularly, but not exclusively, a xenobiotic or steriod, on the regulation of expression of the CYP3A4 gene in a human.

TRANSGENIC ANIMALS FOR ANALYSING CYP3A4 CYTOCHROME P450 GENE REGULATION

TECHNICAL FIELD OF THE INVENTION

5   The invention relates to the generation of a transgenic
animal and to the use of the animal for determining the
effect of a compound, particularly, but not exclusively, a
xenobiotic or steroid, on the regulation of expression of
a P450 gene in a human.

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BACKGROUND OF THE INVENTION

Many endogenous and exogenous compounds are observed to
have a therapeutic effect in drug development trials *in
vitro*. However, the intended therapeutic effect is often
15   not realised in clinical practice, for example, when
compounds are co-administered, because certain compounds
induce the expression of the CYP3A4 gene. This induction
generates CYP3A4 cytochrome P450 molecules which
metabolise compounds before the intended therapeutic
20   effect of each compound can be realised. Accordingly,
induction of expression of the CYP3A4 gene interferes with
intended dosage, leading to therapeutic failure or sub-
optimal treatment.

25   Induction of CYP3A4 gene expression is a significant
problem for drug development because time, resources and
expense are wasted in the development of candidate drugs
for therapy of particular disease conditions which will
ultimately fail or perform sub-optimally in clinical
30   practice.

It would be advantageous to have an animal model for use
in drug development trials from which, at an early stage
of drug development, one could determine whether a

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candidate drug would be likely to achieve an intended
therapeutic effect in a human.

Such an animal model would not be useful unless at least
5   some of the aspects of the regulation of CYP3A4 gene
expression in the human, especially tissue specific
expression, are reproduced. This is because in the human,
the CYP3A4 gene is expressed in specific tissues,
including liver and small intestine, which many compounds
10 inevitably come into contact with when administered for
the purpose of therapy. Accordingly, one would be unable
to determine whether the bio-availability of a candidate
drug would be sufficient for achieving an intended
therapeutic effect in clinical practice in a model which
15 does not reproduce the constitutive and xenobiotic induced
tissue specific expression of the CYP3A4 gene that is
observed in the human.

WO99/61622 and Goodwin et al. 1999 disclose a nucleic acid
20 molecule located 8 kb upstream from the initiation of
transcription site of the CYP3A4 gene which regulates
transcription of the CYP3A4 gene in response to xenobiotic
compounds. These documents do not disclose elements for
regulating the constitutive and xenobiotic inducible
25 tissue specific and developmental expression of the CYP3A4
gene observed in a human.

There is a need for an animal model which reproduces at
least some aspects of the expression of the CYP3A4 gene in
30 a human, for determining whether a compound, for example,
one identified in a drug development trial, would be
likely to induce CYP3A4, and hence cause drug-drug
interactions, or auto-induction of the metabolism of the
drug under study.

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DESCRIPTION OF THE INVENTION

The invention seeks to address the above identified need
and in a first aspect provides a non-human mammal
comprising:

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(a)   a regulatory nucleic acid molecule which is capable
of regulating transcription of the human CYP3A4 gene and
which comprises a nucleotide sequence that is identical to
a sequence of the human CYP3A4 gene located between the
10   initiation of transcription site of the gene and a
position located at least 13,000 nucleotides upstream from
the site; and

(b)   a reporter nucleic acid molecule for producing a
15   detectable amount of a reporter molecule for indicating
regulation of transcription of the reporter nucleic acid
molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules
20   are arranged to permit the regulatory nucleic acid
molecule to regulate transcription of the reporter nucleic
acid molecule.

As described herein, the inventors have found that the
25   incorporation of a region of the human CYP3A4 gene that is
located between the initiation of transcription site of
the gene and a position 13,000 nucleotides upstream of the
initiation of transcription site into an animal model
provides the animal with sufficient genetic information
30   for reproducing the constitutive and xenobiotic induced
tissue specific expression of the CYP3A4 gene that is
observed in humans. More specifically, the inventors have
generated animal models which contain a transgene
comprising this region and have observed that these models
35   provide constitutive and xenobiotic inducible expression
of a transgene in a tissue pattern which reproduces the

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tissue specific expression of CYP3A4 which is observed in
a human. Importantly, the level of constitutive
expression is sufficient to allow one to observe the
effect on the regulation of tissue specific transgene
5   expression, of administration of a compound, for example,
a xenobiotic or steroid, to the animal.

Further, the inventors have observed that the animal
models described herein also reproduce aspects of the
10   constitutive and xenobiotic inducible developmental
expression of the CYP3A4 gene that is observed in humans.

These findings are unanticipated because prior to the
invention, there was no suggestion that the genetic
15   information required for simulating the constitutive and
xenobiotic induced tissue specific or developmental
expression of the CYP3A4 gene that is observed in a human
would be contained in the region of the human CYP3A4 gene
between the initiation of transcription site of the gene
20   and a position 13,000 nucleotides upstream of the
initiation of transcription site.

Further, prior to the invention, differences in the
induction profile of the mouse CYP3A11 and the human
25   CYP3A4 gene had been observed, and differences had also
been observed in the ligand binding profile of mouse
transcription factors, especially PXR and CAR, and human
PXR and CAR. Accordingly, there was no suggestion that a
non-human animal would have factors sufficient for
30   interacting with a region of the CYP3A4 gene for
reproducing the constitutive and xenobiotic induced tissue
specific or developmental expression of CYP3A4 observed in
a human.

35   Further, prior to the invention, mechanisms associated
with transgene integration had been observed, such as gene

silencing and mosaic transgene expression which limited
the extent to which an a transcriptional enhancer element
incorporated into a trangenic model could reproduce
regulation of gene expression observed in a human.
5   Accordingly, there was no suggestion that a region of the
human CYP3A4 gene would be capable of reproducing the
regulation of expression of the CYP3A4 gene that is
observed in a human. However, as described herein, the
inventors have shown in 2 separate founder lines that the
10 expression of the transgene reproduces aspects of CYP3A4
gene expression that are observed in humans.

Thus in a second aspect, the invention provides a non
human mammal comprising:

15

(a)   a regulatory nucleic acid molecule comprising a
nucleotide sequence that is identical to the nucleotide
sequence of the human CYP3A4 gene that extends about
13,000 nucleotides upstream from the initiation of
20 transcription site of the gene; and

(b)   a reporter nucleic acid molecule for producing a
detectable amount of a reporter molecule for indicating
regulation of transcription of the reporter nucleic acid
25 molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules
are arranged to permit the regulatory nucleic acid
molecule to regulate transcription of the reporter nucleic
30 acid molecule.

In one embodiment, the regulatory nucleic acid molecule
comprises the sequence shown in SEQ ID NO:1.

35 Further, as described herein, the inventors have generated
transgenic animals which contain a region of the human

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CYP3A4 gene between the initiation of transcription site and a position about 3,200 nucleotides upstream of the initiation transcription site and observed that the transgene is not constitutively expressed or inducible by
5 xenobiotics in these animals. Accordingly, the inventors have found that the genetic information required for reproducing the constitutive and xenobiotic induced tissue specific and developmental expression of CYP3A4 observed in a human is contained in the region of the human CYP3A4
10 gene between the position located about 3,200 nucleotides upstream of the initiation of transcription site of the gene and a position 13,000 nucleotides upstream of the initiation of transcription site.

15 Thus, in a third aspect, the invention provides a non-human mammal comprising:

   (a)   a regulatory nucleic acid molecule comprising a nucleotide sequence that is identical to the sequence of
20 the human CYP3A4 gene that extends about 8,000 nucleotides upstream from a position about 3,000 nucleotides upstream from the initiation of transcription site of the gene; and

   (b)   a reporter nucleic acid molecule for producing a
25 detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules
30 are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

In one embodiment, the regulatory nucleic acid molecule
35 comprises the sequence shown in SEQ ID NO:2.

In a fourth aspect, the invention provides a non-human
mammal comprising:

5   (a)   a regulatory nucleic acid molecule which is capable
of regulating transcription of the human CYP3A4 gene and
which comprises a nucleotide sequence that is identical to
the sequence of the human CYP3A4 gene that extends about
600 nucleotides upstream from a position about 7,200
nucleotides upstream of the initiation of transcription
10 site of the gene; and

(b)   a reporter nucleic acid molecule for producing a
detectable amount of a reporter molecule for indicating
regulation of transcription of the reporter nucleic acid
15 molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules
are arranged to permit the regulatory nucleic acid
molecule to regulate transcription of the reporter nucleic
20 acid molecule.

In one embodiment, the regulatory nucleic acid molecule
comprises the sequence shown in SEQ ID NO:3.

25 In another embodiment, the regulatory nucleic acid
molecule has the sequence of any one of the following
fragments of the CYP3A4 gene:
(i) a fragment consisting of from nucleotide positions
-13,000 to +53;
30 (ii) a fragment consisting of from nucleotide positions
-13,000 to -12,700 contiguous with -8000 to +53;
(iii) a fragment consisting of from nucleotide positions
-13,000 to -5,100 contiguous with -1,200 to +53;
(v) a fragment consisting of from nucleotide positions
35 -7,800 to -6,000 contiguous with -362 to +53;
(vi) a fragment consisting of from nucleotide positions

-7,500 to -6,000 contiguous with -362 to +53;

A regulatory nucleic acid molecule which has the sequence
of a fragment consisting of from nucleotide positions
5   -7836 to -7207 contiguous with -362 to +53 is particularly
preferred, as this construct contains the minimal
sequences necessary for regulating transcription of the
human CYP3A4 gene, more specifically, an element
responsive to xenobiotics (the "Xenobiotic Response
10   Element Module" or "XREM") and the proximal promoter of
the CYP3A4 gene.

The regulatory nucleic acid molecule of the invention
typically contains at least one enhancer capable of
15   regulating transcription of a human CYP3A4 gene when
contacted with a nuclear receptor. Examples of such
enhancers are those capable of regulating transcription of
a human CYP3A4 gene when contacted with a nuclear receptor
bound to a ligand, such as a xenobiotic or steroid. Other
20   examples are those capable of regulating transcription of
a human CYP3A4 gene when contacted with a nuclear receptor
consisting of a heterodimer of PXR (pregnane X receptor,
otherwise known as SXR (steroid and xenobiotic receptor))
and RXR (9-cis retinoic acid receptor), or CAR
25   (constitutive androstane receptor-β) and RXR.

The inventors believe that certain nucleic acid molecules
which have substantially the same nucleotide sequence as a
regulatory nucleic acid molecule of the invention would
30   also have sufficient genetic information for reproducing
the constitutive and xenobiotic induced tissue specific
and developmental expression of the CYP3A4 gene that is
observed in a human. Accordingly, it will be understood
that nucleotides could be modified or deleted in regions'
35   of the regulatory nucleic acid molecule, more
specifically, those regions which do not contain an

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enhancer such as those described above, without
significantly limiting the capacity of the molecule to
regulate transcription of the human CYP3A4 gene.

5   The inventors recognise that it would be advantageous to
       provide an animal model further capable of reproducing the
       expression of other human genes, specifically those genes
       encoding products which modify or modulate the therapeutic
       activity of exogenous and endogenous compounds used for
10   therapy and cause drug-drug interactions, for example,
       cytochrome P450 genes or ABC transporter superfamily
       genes, for example, P-glycoprotein (otherwise known as
       MDR-1). The regions controlling the constitutive and
       xenobiotic induced tissue specific expression of some of
15   these genes are known, and in some instances, non-human
       animal models have been generated. The inventors recognise
       that the genetic background of these animals could be
       incorporated into the non-human mammal of the present
       invention, for example, by conventional breeding
20   techniques.

       Thus in a fifth aspect, the invention provides a non-human
       mammal of any one of the first to fourth aspects of the
       invention, further comprising:
25
       (c)   a further regulatory nucleic acid molecule which is
       capable of regulating transcription of a human gene; and

       (d)   a further reporter nucleic acid molecule for
30   producing a detectable amount of a further reporter
       molecule for indicating regulation of transcription of the
       further reporter nucleic acid molecule by the further
       regulatory nucleic acid molecule

35   wherein the further reporter and further regulatory
       nucleic acid molecules are arranged to permit the further

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regulatory nucleic acid molecule to regulate transcription
of the further reporter nucleic acid molecule.

In one embodiment, the at least one further regulatory
5   nucleic acid molecule has a sequence shown in SEQ ID NO:4.
In another embodiment, the at least one further regulatory
nucleic acid molecule has a sequence shown in SEQ ID NO:5.

Although the regulatory nucleic acid molecule of the
10   invention described herein is sufficient for reproducing
the constitutive tissue specific and developmental
expression of the CYP3A4 gene that is observed in a human,
the inventors recognise that aspects of the xenobiotic
inducibility of the gene could be better reproduced in an
15   animal by incorporating at least one human transcription
factor that is capable of interacting with the regulatory
nucleic acid molecule for regulating transcription of the
human CYP3A4 gene. Examples of such factors are nuclear
receptors. These receptors may be those capable of
20   regulating CYP3A4 gene transcription in a human when the
receptor is bound to a ligand, such as a xenobiotic or
steroid. One example of such a receptor is the human PXR
(pregnane X receptor, otherwise known as SXR (steroid and
xenobiotic receptor)). Another suitable receptor is the
25   human CAR (constitutive androstane receptor-β). Non-human
animals comprising a human PXR or CAR receptor are known.
The inventors recognise that the genetic background of
these animals could be incorporated into the non-human
mammal of the present invention, for example, by
30   conventional breeding techniques.

Thus in a sixth aspect, the non-human animal of the
invention further comprises at least one human
transcription factor for regulating transcription of a
35   human CYP3A4 gene. Preferably the transcription factor is
a nuclear receptor. Preferably, the nuclear receptor is a

heterodimer of the human PXR (pregnane X receptor,
otherwise known as SXR (steroid and xenobiotic receptor))
and human RXR (9-cis retinoic acid receptor) or human CAR
(constitutive androstane receptor-β) and human RXR.

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It follows that the reporter nucleic acid molecule can be
any molecule which is capable of detection when the
reporter nucleic acid molecule is transcribed. For
example, the reporter nucleic acid molecule could be the
10   CYP3A4 cytochrome, or the mRNA transcript which is .
translated to produce the cytochrome. Those reporter
molecules which are commercially available, including
firefly luciferase, β- galactosidase, alkaline phosphatase,
green fluorescent protein or chloramphenicol acetyl
15   transferase can be used.

Thus in one embodiment, the reporter nucleic acid molecule
is capable of producing a reporter molecule selected from
the group of reporter molecules consisting of firefly
20   luciferase, β-galactosidase, alkaline phosphatase, green
fluorescent protein or chloramphenicol acetyl transferase.

While the non-human mammal of the invention, as
exemplified below, is a mouse, the inventors believe that
25   any other non-human mammal could be used in the invention,
especially those for which standard transgenic techniques
have been developed including for example, rat and rabbit.
However, typically the non-human mammal is a mouse.

30   In another aspect, the invention provides a tissue of a
non-human mammal of the invention.

In one embodiment, the tissue is an embryo capable of
producing a non-human mammal of the invention.

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In a further aspect, the invention provides a method of
determining whether a compound is capable of effecting the
transcription of a human CYP3A4 gene the method comprising
the following steps:

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(a)   administering the compound to a non human mammal
according to the invention and
(b)   determining whether the reporter molecule is produced
by the reporter nucleic acid molecule in the mammal.

10

In one embodiment, the production of the reporter molecule
indicates that the binding compound is capable of
effecting the transcription of the human CYP3A4 gene.

15   Any compound can be tested in the method however,
preferred compounds are xenobiotic or steroid compounds.

The inventors recognise that a non human animal which
comprises a 5' flanking region of CYP3A4 gene but which is
20   deficient for the region from -7836 to -7207 would be
useful as a negative control in a method for determining
whether a compound is capable of regulating transcription
of the human CYP3A4 gene.

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BRIEF DESCRIPTION OF THE FIGURES

Figure 1. CYP3A4/lacZ transgene constructs used to generate
transgenic mice. The upstream regions of the human CYP3A4
30   gene are depicted as open boxes with the position of the
XREM at approximately -7.5kb of the CYP3A4 gene indicated
by cross-hatching. The 5'-flanking region extended from
56bp downstream of the transcription initiation site to a
HindIII site at -3,213 in the construct designated -
35   3CYP3A4/lacZ and to a KpnI site at -12,926 kb in construct

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-13CYP3A4/lacZ. The coding region of the E.coli lacZ gene
together with eukaryotic translational initiation and
termination signals, transcription termination and poly
adenylation sites are indicated by a solid box.

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Figure 2. Xenobiotic induction of hepatic transgene
expression. Female mice from line 9/4 harbouring the -
13CYP3A4/lacZ transgene were treated with various reagents.
Histochemical staining of liver slices with X-gal revealed
10   an increased zone of blue staining cells containing β-
galactosidase after treatment with rifampicin,
phenobarbital and pregnenolone 16α-carbonitrile compared
with corn oil treated mice.

15   Figure 3. Comparison of the xenobiotic induction profile
of the -13CYP3A4/lacZ transgene with the mouse Cyp3a11
gene. Transgenic mice from line 9/4 were treated with a
range of xenobiotic reagents and naturally occurring
steroids. A. Transgene expression was assessed by
20   determining β-galactosidase activity in total liver lysates
using the ONPG assay. The units of β-galactosidase activity
are given as A_{420}/mg liver/minute. Dexamethasone and
pregnenolone 16α-carbonitrile were the most potent
xenobiotic activators of the -13CYP3A4/lacZ transgene,
25   while rifampicin treatment resulted in relatively low
levels. The steroids pregnenolone and 17α-progesterone
were very weak inducers. B. Hepatic expression of the
endogenous mouse Cyp3a11 gene was examined in the same mice
by Northern analysis. A similar pattern of induction to
30   the CYP3A4/lacZ transgene was observed with both xenobiotic
and endogenous regulators. The data are presented as the
mean +/- the standard deviation for 3 animals.

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Figure 4. Dose response of -13CYP3A4/*lacZ* transgene
expression after treatment with dexamethasone. A. Male
mice from line 9/4 were treated with from 1 to 100mg/kg
5   dexamethasone. Higher doses of dexamethasone resulted in
increased β-galactosidase activity (determined in liver
lysates as described in Fig. 3).B. Zonal expansion of
transgene expression with increasing doses of
dexamethasone. X-gal staining of frozen liver sections
10   revealed greater numbers of hepatocytes containing
transgene-derived β-galactosidase activity after treatment
with 1, 10 and 100 mg/kg dexamethasone. At low doses there
are limited numbers of transgene -expressing cells
immediately adjacent to the central vein. With higher
15   doses there are more cells committed to transgene
expression extending across the liver lobule towards the
portal tract.

Figure 5. (SEQ ID NO:1) Sequence of the CYP3A4 5'-flanking
20   region included in the -13 CYP3A4/lacZ construct. This
sequence corresponds to -12,926 to +56 base pairs relative
to the transcription initiation site of the CYP3A4 gene.

Figure 6.   (SEQ ID NO:2)Sequence of the 5'-flanking region
25   of the CYP3A4 gene extending from -12,926 to -3,213 base
pairs and representing the difference in sequence between
the -13 CYP3A4/lacZ and the -3 CYP3A4/lacZ constructs.

Figure 7.   (SEQ ID NO:3)The "Xenobiotic-Responsive
30   Enhancer Module" (XREM) of the human CYP3A4 gene. This
region encompasses -7836 to -7207 base pairs relative to
the transcription initiation site of the CYP3A4 gene.

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Figure 8.   (SEQ ID NO:4)The 5'-flanking region of the
human CYP3A7 gene (Genbank Accession No. AF329900). The
extent of the sequences is -11,133 to +52 base relative to
5   the transcription initiation site of the CYP3A7 gene.

Figure 9.   (SEQ ID NO:5)Sequence of the 5'-flanking region
of the human MDR1 gene (p-glycoprotein gene) encompassing -
10,000 to +200 base pairs relative to the transcription
10   initiation site of the MDR1 gene. Sequence derived from
within Genbank sequence Accession Number AC002457.

An embodiment of the invention is now described in the
following Example which will be understood to merely
15   exemplify and not to limit the scope of the invention.

EXAMPLE

MATERIALS AND METHODS

Transgene constructs.   Two transgene constructs were
20   synthesized with the upstream 5' flank of the human
cytochrome P450 *CYP3A4* gene linked to the E. coli *lacZ*
reporter gene (Figure 1).   The first construct, designated
-3CYP3A4/*lacZ*, contained the region of the *CYP3A4* gene from
the HindIII site at -3213bp relative to the transcription
25   start site to nucleotide +56bp downstream of the
transcription start site.   The other construct, designated
-13CYP3A4/*lacZ*, included the region of the CYP3A4 gene from
the KpnI site at -12,926bp upstream to +56bp downstream of
the transcription start site.   It includes the DNA
30   sequences of the XREM region located between -7836 and -
7208 in addition to the proximal promoter of the *CYP3A4*
gene.   The DNA sequence of the *CYP3A4* gene between -10468bp
and +906bp has been determined and deposited with the

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GenBank/EMBL/DDJB database under accession number AF185589.
Additional sequence information covering the region -
10,469bp to -12,926bp was obtained from publically
accessible Genbank files. The E.coli *lacZ* reporter gene

5   comprises the coding region for the bacterial enzyme β-
galactosidase flanked by DNA sequences for eukaryotic
translational start and stop signals, SV40 transcriptional
termination and polyadenylation signals and an intron. The
CYP3A4/lacZ transgene constructs were released from vector

10 sequences and purified on agarose gels prior to
microinjection
Generation of transgenic mouse lines. Mice carrying the
CYP3A4/*lacZ* transgenes were created by microinjection of
the DNA constructs into the pro-nuclei of zygotes harvested

15 from FVB/N strain mice. Microinjection and manipulation of
embryos were carried by standard techniques. Stable
transgenic mouse lines were established by breeding from
transgenic founders identified by Southern analysis.
Administration of xenobiotics to mice. 8-10 week old male

20 and female mice hemizygous for the -3CYP3A4/*lacZ* and -
13CYP3A4/*lacZ* transgenes were used to test the ability of a
range of xenobiotics and hormones to activate expression of
transgene-derived β-galactosidase. Mice were administered
the following reagents and vehicles by single daily

25 intraperitoneal injection for 4 days: rifampicin/corn oil;
dexamethasone phosphate/H_2O; pregnenolone 16α-
carbonitrile/2% Tween 20 in H_2O; phenobarbital/H_2O;
clotrimazole/2% Tween 20; phenytoin/2% Tween 20; 17α-OH
progesterone/2% Tween 20; pregnenolone/2% Tween 20. All

30 reagents were supplied by Sigma Chemical Co. (St Louis, MO)
except for dexamethasone phosphate which was obtained from
Faulding (Mulgrave, Australia) and pregnenolone 16α-

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carbonitrile from Upjohn Co. (Kalamazoo, MI). The dose used
for all reagents to test for induction of the transgene was
100mg/kg body weight. Dose response studies were carried
out in the range of 1-100mg/kg with male hemizygous

5   transgenic mice.
    Analysis of transgene and mouse Cyp3a gene expression. β-
    galactosidase activity was visualised in slices and frozen
    sections of liver and other tissues by staining with X-gal
    (5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside).

10. Tissues were fixed in 0.25% glutaraldehyde, 0.1M phosphate
    buffer pH7.3, 5mM EGTA, 2 mM $MgCl_2$: washed in 0.1M
    phosphate buffer pH7.3, 0.01%sodium deoxycholate, 0.025%
    NP40, 2mM $MgCl_2$ and stained by incubation at 37°C in wash
    solution supplemented with 1mg/ml X-gal, 5mM potassium

15 ferricyanide, and 5mM potassium ferrocyanide. The level of
    β-galactosidase activity was determined in whole liver
    homogenates [100mg fresh tissue/ml 0.25M Tris-HCl (pH 7.3)]
    using the O-nitrophenyl-β-D-galactopyranoside (ONPG) assay
    according to standard techniques. After appropriate

20 dilution the homogenate was incubated with β-galactosidase
    assay reagent (0.1M sodium phosphate buffer (pH7.3)/1mM
    $MgCl_2$/50 mmol β-mercaptoethanol/0.88mg/ml ONPG) at 37°C,
    quenched by the addition of 1M Na_2CO_3 and the absorbance at
    420nm determined. The units of β-galactosidase activity

25 are given as A_{420}/mg liver/minute.
    The levels of endogenous mouse Cyp3a mRNA expression were
    determined by Northern analysis using a riboprobe
    complementary to nucleotides 852-1061 of the mouse Cyp3a11
    cDNA. Filters were stripped and reprobed with an 18S rRNA

30 oligonucleotide to normalise loading.

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RESULTS

4 transgenic lines were generated with the construct
containing the -3.2kb region of the human *CYP3A4* gene
linked to *lacZ*. Transgene-derived β-galactosidase activity

5   was not detected in kidney, large and small intestine,
spleen, lung and liver tissue from mice for all 4 -
3CYP3A4/*lacZ* transgenic lines treated with vehicle or
xenobiotics (Table 1). In contrast, transgene expression
was readily detected in 3 of the 4 lines carrying the -

10   13CYP3A4/*lacZ* construct. Line 9/4 had a very low
constitutive level in the liver, with β-galactosidase
detected only in isolated hepatocytes adjacent to major
blood vessels. Administration of xenobiotics resulted in
robust expression in a zone of cells surrounding the

15   central vein (Figure 2). As the basal level of transgene
expression in untreated mice in line 9/4 is extremely low,
induction is obvious and is essentially an off/on process.
Expression in other tissues in mice from line 9/4 was
restricted to the gut, predominantly in the villi of the

20   small intestine.
The relative degree of induction for a range of xenobiotics
was analysed by determining the transgenic β-galactosidase
activity in liver lysates of mice from line 9/4 (Figure
3A). Dexamethasone and pregnenolone 16α-carbonitrile were

25   the most potent inducers, while rifampicin activated the
transgene to relatively modest levels. Phenobarbital,
clotrimazole and phenytoin were intermediate inducers. The
induction profile of the transgene in line 9/4 was similar
to that observed for the endogenous *Cyp3a11* gene in the

30   same mice (Fig 3B), likely reflecting the activation
profile of the mouse rather than the human PXR. Activation
of the transgene was observed with naturally occurring

steroids such as pregnenolone and 17α-progesterone, however
the induction was weak compared with xenobiotics.

There was a marked gender difference in hepatic transgene
expression, with lower levels observed in females than in

5   males for most reagents. Such a male-predominant pattern
was not evident in the induction profile of the mouse
Cyp3a11 gene. Indeed higher levels of Cyp3a11 mRNA were
observed in females than males after treatment with
rifampicin and pregnenolone 16α-carbonitrile. The reason

10   for this apparent reversal in gender-related transgene
expression pattern is not known. However, as Cyp3a11 mRNA
is only just detectable in males of the FVB/N strain of
mice, it may be attributed to the relatively greater degree
of induction of the mouse *Cyp3a11* gene in males compared to

15   females (Figure 3B).

The other line which showed significant transgene
expression - 15/10, had a higher constitutive level in both
the liver and small intestine in untreated mice.
Expression was not detected in other organs, confirming the

20   tissue specificity observed in line 9/4. The same set of
reagents were capable of increasing hepatic and intestinal
transgene expression to the same levels as in mice from
line 9/4. However, the overall degree of induction was not
as great as observed in line 9/4 due to the higher basal

25   level in line 15/10. The induction profile was similar
with dexamethasone being the most potent activator and
rifampicin the least (data not shown).

Dose response of xenobiotic induction. The activation of
transgene expression in line 9/4 by dexamethasone was dose-

30   dependent over the range 1 to 100 mg/kg (Figure 4A). The
higher transgene-derived β-galactosidase activity in liver
homogenates from mice treated with increasing doses of

dexamethasone was associated with an expanded zone of cells
which were stained by X-gal. At low doses of dexamethasone
a ring of hepatocytes only 1-2 cells thick around the
central vein expressed the transgene (Figure 4B). With

5   100mg/kg dexamethasone the zone of X-gal positive
hepatocytes increased to up to 10 cells, approximately
midway between the central vein and the portal triad. A
similar dose-dependent expansion of hepatocytes expressing
the transgene was observed with other reagents and also in

10   line 15/10 which also contained the -13CYP3A4/lacZ
construct.

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CLAIMS

1.   A non-human mammal comprising:
        (a)   a regulatory nucleic acid molecule which is
        capable of regulating transcription of the human
        CYP3A4 gene and which comprises a nucleotide sequence
        that is identical to a sequence of the human CYP3A4
        gene located between the initiation of transcription
        site of the gene and a position located at least
        13,000 nucleotides upstream from the site; and
        (b)   a reporter nucleic acid molecule for producing
        a detectable amount of a reporter molecule for
        indicating regulation of transcription of the
        reporter nucleic acid molecule by the regulatory
        nucleic acid molecule;
        wherein the reporter and regulatory nucleic acid
        molecules are arranged to permit the regulatory
        nucleic acid molecule to regulate transcription of
        the reporter nucleic acid molecule.

2.   A non human mammal comprising:
        (a)   a regulatory nucleic acid molecule comprising a
        nucleotide sequence that is identical to the
        nucleotide sequence of the human CYP3A4 gene that
        extends about 13,000 nucleotides upstream from the
        initiation of transcription site of the gene; and
        (b)   a reporter nucleic acid molecule for producing
        a detectable amount of a reporter molecule for
        indicating regulation of transcription of the
        reporter nucleic acid molecule by the regulatory
        nucleic acid molecule;
        wherein the reporter and regulatory nucleic acid
        molecules are arranged to permit the regulatory
        nucleic acid molecule to regulate transcription of
        the reporter nucleic acid molecule.

3.   A mammal according to claim 2 wherein the regulatory
        nucleic acid molecule comprises the sequence shown in
        SEQ ID NO:1.

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4.   A non-human mammal comprising:
        (a)   a regulatory nucleic acid molecule comprising a
        nucleotide sequence that is identical to the sequence
        of the human CYP3A4 gene that extends about 8,000
5   nucleotides upstream from a position about 3,000
        nucleotides upstream from the initiation of
        transcription site of the gene; and
        (b)   a reporter nucleic acid molecule for producing
        a detectable amount of a reporter molecule for
10   indicating regulation of transcription of the
        reporter nucleic acid molecule by the regulatory
        nucleic acid molecule;
        wherein the reporter and regulatory nucleic acid
        molecules are arranged to permit the regulatory
15   nucleic acid molecule to regulate transcription of
        the reporter nucleic acid molecule.

5.   A mammal according to claim 4 wherein the regulatory
        nucleic acid molecule comprises the sequence shown
        SEQ ID NO:2.

20 6.   A non-human mammal comprising:
        (a)   a regulatory nucleic acid molecule which is
        capable of regulating transcription of the human
        CYP3A4 gene and which comprises a nucleotide sequence
        that is identical to the sequence of the human CYP3A4
25   gene that extends about 600 nucleotides upstream from
        a position about 7,200 nucleotides upstream of the
        initiation of transcription site of the gene; and
        (b)   a reporter nucleic acid molecule for producing
        a detectable amount of a reporter molecule for
30   indicating regulation of transcription of the
        reporter nucleic acid molecule by the regulatory
        nucleic acid molecule;
        wherein the reporter and regulatory nucleic acid
        molecules are arranged to permit the regulatory
35   nucleic acid molecule to regulate transcription of
        the reporter nucleic acid molecule.

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7.   A mammal according to claim 6 wherein the regulatory
      nucleic acid molecule comprises the sequence shown in
      SEQ ID NO:3.

8.   A mammal according to any one of the preceding claims
5   wherein the regulatory nucleic acid molecule has the
      sequence of a fragment of the CYP3A4 gene consisting
      of from nucleotide positions -7836 to -7207
      contiguous with -362 to +53.

9.   A mammal according to any one of the preceding
10   claims, further comprising:
      (c) a further regulatory nucleic acid molecule
      which is capable of regulating transcription of a
      human gene; and
      (d)   a further reporter nucleic acid molecule for
15   producing a detectable amount of a further reporter
      molecule for indicating regulation of transcription
      of the further reporter nucleic acid molecule by the
      further regulatory nucleic acid molecule;
      wherein the further reporter and further regulatory
20   nucleic acid molecules are arranged to permit the
      further regulatory nucleic acid molecule to regulate
      transcription of the further reporter nucleic acid
      molecule.

10.   A mammal according to claim 9 wherein the at least
25   one further regulatory nucleic acid molecule has a
      sequence shown in SEQ ID NO:4.

11.   A mammal according to claim 9 wherein the at least
      one further regulatory nucleic acid molecule has a
      sequence shown in SEQ ID NO:5.

30 12.   A mammal according to any one of the preceding
      claims, further comprising at least one human
      transcription factor for regulating transcription of
      a human CYP3A4 gene.

13.   A mammal according to claim 12 wherein the
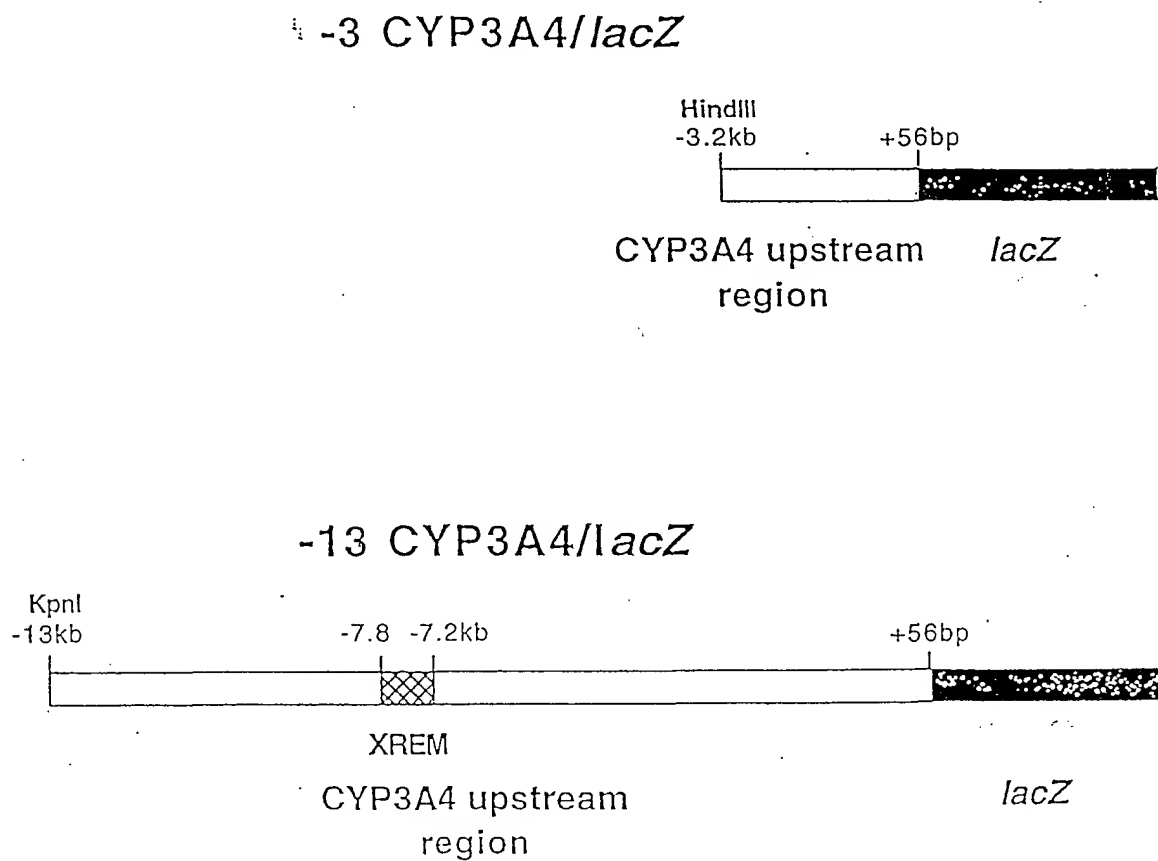35   transcription factor is a nuclear receptor.

14.   A mammal according to claim 13 wherein the nuclear receptor is a heterodimer of the human pregnane X receptor and human 9-cis retinoic acid receptor or a heterodimer of human constitutive androstane

5   receptor-β and human 9-cis retinoic acid receptor.

15.   A mammal according to any one of the preceding claims wherein the reporter nucleic acid molecule is capable of producing a reporter molecule selected from the group of reporter molecules consisting of firefly

10   luciferase, β-galactosidase, alkaline phosphatase, green fluorescent protein or chloramphenicol acetyl transferase.

16.   A mammal according to any one of the preceding claims wherein the mammal is a mouse.

15   17.   A tissue of a mammal according to any one of the preceding claims.

18.   A tissue according to claim 17 wherein the tissue is an embryo capable of producing a mammal according to any one of the preceding claims.

20   19.   A method of determining whether a compound is capable of effecting the transcription of a human CYP3A4 gene the method comprising the following steps:

     (a)   administering the compound to a non human mammal according to any one of the preceding

25   claims; and

     (b)   determining whether the reporter molecule is produced by the reporter nucleic acid molecule in the mammal.

20.   A method according to claim 19 wherein the production

30   of the reporter molecule indicates that the binding compound is capable of effecting the transcription of the human CYP3A4 gene.

Table 1. Expression of CYP3A4/lacZ transgenic lines

Construct	Line No.	Copy No.	LIVER		Small Intestine
			Basal	Inducible	
-3CYP3A4/ lacZ	13	15	-	-	-
	24	>100	-	-	-
	31	80	-	-	-
	39	10	-	-	-
-13CYP3A4/ lacZ	13/5	70	-	-	+
	9/4	5	+	++++	-
	9/7	50	-	+	-
	15/10	8	++	++++	++++

Fig 1. Human CYP3A4/*lacZ* transgene constructs

-3 CYP3A4/*lacZ*

CYP3A4 upstream
region   *lacZ*

-13 CYP3A4/l*acZ*

XREM

CYP3A4 upstream
region   *lacZ*

Figure 2. Xenobiotic induction of CYP3A4/lacZ transgene

Control

Rifampicin

Phenobarbital

Pregnenolone-16α
carbonitrile

Figure 3A. Xenobiotic Induction of CYP3A4/lacZ transgene

Fig 3B Xenobiotic induction of mouse CYP3A11 mRNA
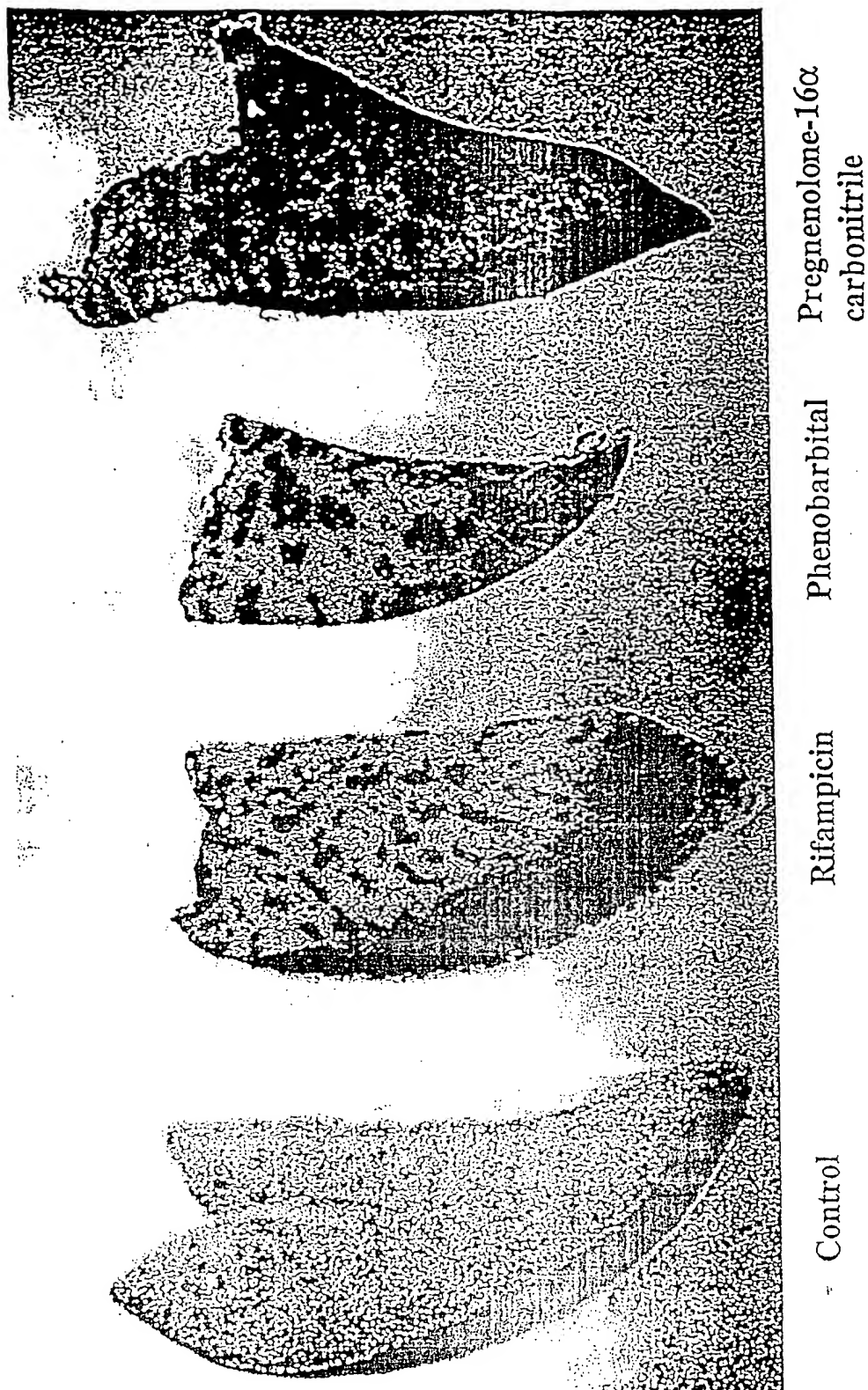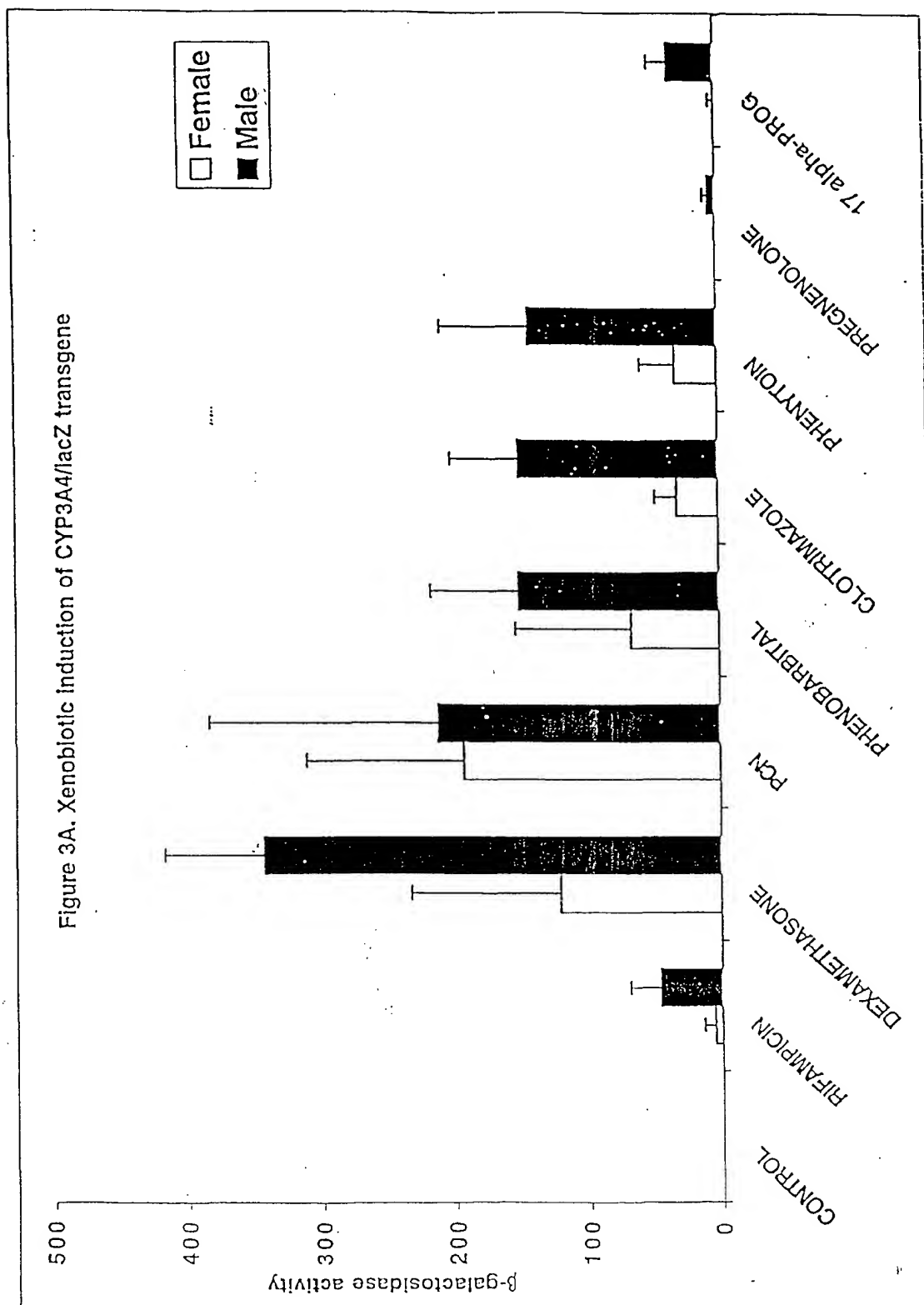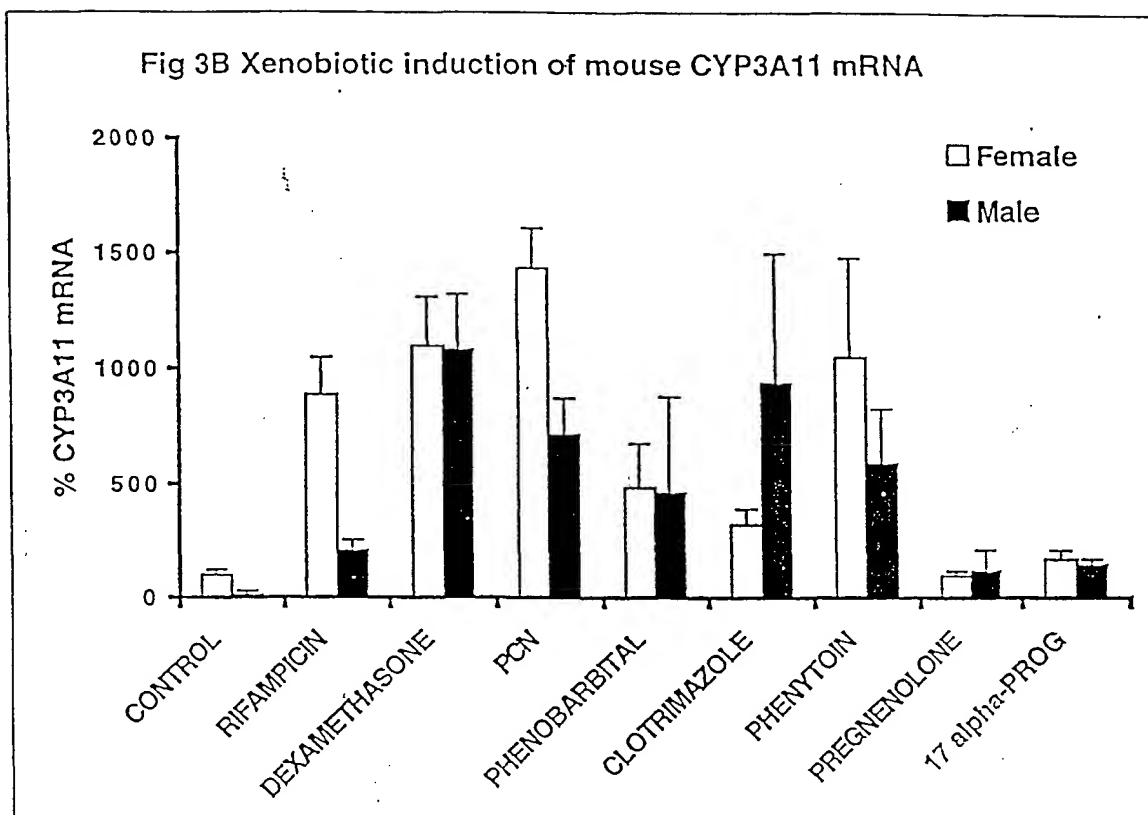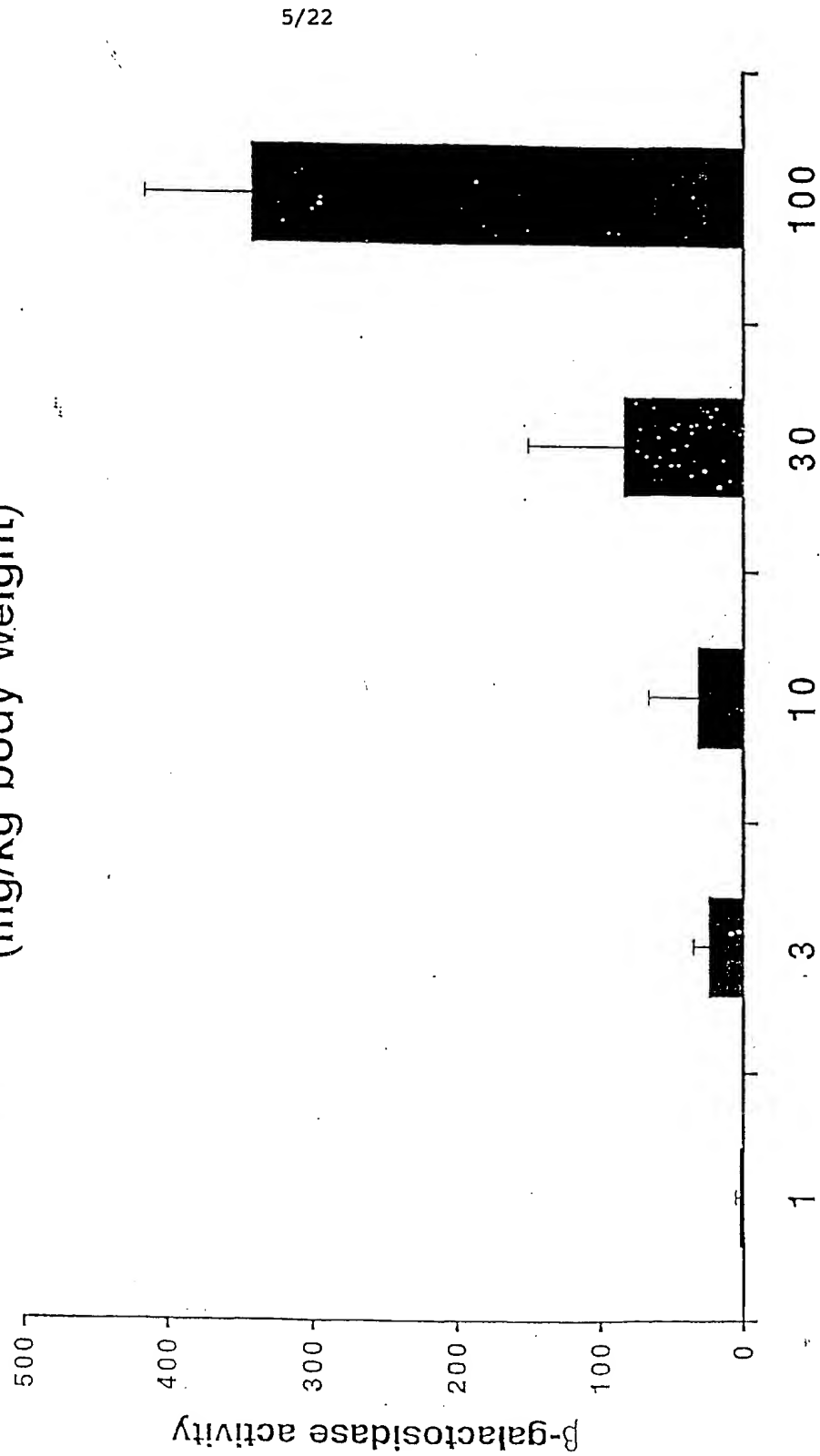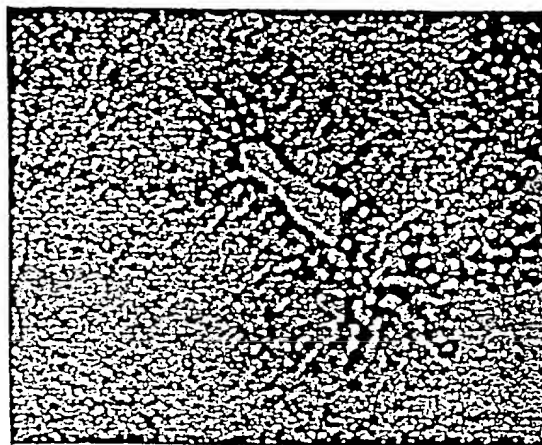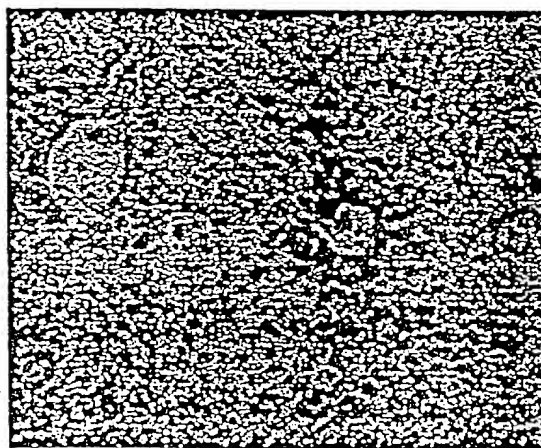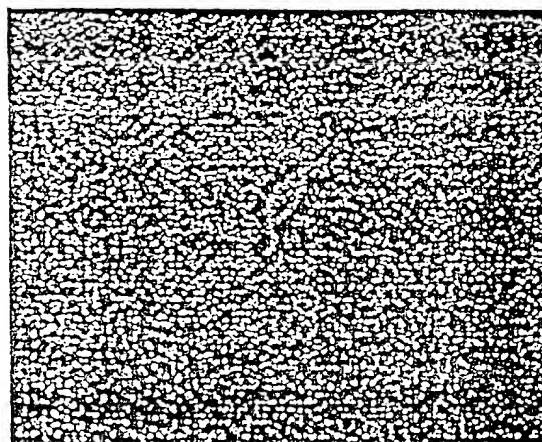
Figure 4A Dexamethasone dose-response (mg/kg body weight)

Figure 4B. Dose response of transgene expression

Figure 5.

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5   TGAGCCTGAGGAACTGTGCACTCTGGCCCAGATACTGCACTTTTCCCATGGTCTTTGCAACCCGCAGACCA

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Figure 6.

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SUBSTITUTE SHEET (RULE 26)

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25   CTGTCTAAATAACAAAAATAATAGTAAAGAAAAGGATTGGGATGCCATTTACTTGCGTATTCAATACACAG
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35   TCTCAGCTGAATGAACTTGCTGACCCTCTGCTTTCCTCCAGCCTCTCGGTGCCCTTGAAATCATGTCGGTT
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40   GGTAGATGCTTTCATCAGATTAAGAAAATTCCCTGCTATTAGTTGTTGAAGGTTTTTATATCATAAATGAA

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5   AGTCCTGATTTTTTTCTGATTGGATCATGTGGTTATGGCCCTCATGGAATGAGTTGGGCATGATGCCTTT
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10  GCACCCACCGACACACCCTGCTAATTTTTGTATTTTTAGTACAGATGGGGTTTCACAATATTGGCCAAGCT
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15  AGATGGAAGCTGGGTTGGACCCACTCTATGCTGAAGAACAGCTTGTGTGGACACAAGGAGACACGGATATG
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20  GCAAAACAAGTTAGGGGGTTACTGAAATAAGGAGTATGAGAAATGGTGTAGGTTGTGCTGACGTTTTGTAA
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25  AGCATTTTATAACTACACTGGCAGTGTGCTGGGAGGTGTAGAGAGAAATATTTATCACATGTGTGGCTGAC
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30  GACACTCTAGAATGGAGTAGAAAGCCAACAGTTATGATTGAGTCCTCCTCCTCTTCTTCTTTTTATTAATT
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35  TACCCATTCAGAAGGCCTGGGCTGCACTGCTAGTTCCTCACTAACTCTGTGTGGCCTTGGGCAAGGTTGGG
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CATGACACGTATTCACTATCATTTCCTGGAGTAAGAGCTGTGTGTGAGTGGGTGTGAGCATGTGTGAAACC
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40  TTTTCTCTGCAATCTCAGTTAAGAAACCAATCCAGAATTTAAAGTTCAGGGCCTAAATGGGTGGTTATCTT
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5   CACTTCCCATCTGTCAAGTCTTGTTGATTCTGTTGTATTCATGTCTCTCAAAGGGAGATAGAGTTTAGGGA
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ATCCCAATTTGTAATTCAGTATTATTTGTGTGGCTGTTTGGTGTCTCTTTCTCCTATATGAGTGCTAGCTT
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10   AACCATGCACCTGTCACTCTCCTCAACACCACCCCCAAGCATGAGGCCCAAAAGCATTAGCTAATCCCCTC
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Figure 7.

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5   CATTACAAAG TTTAATTATT TCAGTGATTA TTAAACCTTG TCCTGTGTTG ACCCCAGGTG
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10  CCTGCTATTA GTTGTTGAAG GTTTTTATAT CATAAATGAA AGTTGAATAT TATTATCATA
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```

Figure 8.

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19/22

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Figure 9.

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SUBSTITUTE SHEET (RULE 26)

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Page 19

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1320

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Page 38

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Page 39

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Page 40

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Page 42

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Page 43

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  10200

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A.	CLASSIFICATION OF SUBJECT MATTER

Int. Cl.[7]:   C12N 15/63, 5/10, C12Q 1/68, A01K 67/027, A61K 49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATABASE BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE ELECTRONIC DATABASE BELOW

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Medline, WPIDS, CAPlus. Keywords: CYP3A4, silencer, enhancer, promoter, regulator, regulate, regulating, regulon.

C.	DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/48915, A (GLAXO GROUP LIMITED) 30 September 1999. See page 17 lines 13-18.	1-20
Y	Eur J Drug Metab Pharmacokinet (1997) 22(4):311-3. Ogg MS, Gray TJB, Gibson GG. "Development of an in vitro reporter gene assay to assess xenobiotic induction of the human CYP3A4 gene." See whole document.	1-20
	Note: for the Y indications, WO 99/48915 and Eur J Drug Metab Pharmacokinet (1997) can be combined together.	

[X] Further documents are listed in the continuation of Box C   [X] See patent family annex

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2001	2 4 DEC 2001
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	J.H. CHAN Telephone No : (02) 6283 2340

C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Cancer Chemother Pharmacol (1998) 42 Suppl:S50-3. Kamataki T, Yokoi T, Fujita K, Ando Y. "Preclinical approach for identifying drug interactions." See whole document.	
A	Chem Biol Interact (1997) 107(1-2):93-108. Olsen AK, Hansen KT, Friis C. "Pig hepatocytes as an in vitro model to study the regulation of human CYP3A4: prediction of drug-drug interactions with 17 alpha-ethynylestradiol." See whole document.	
A	WO 99/61622, A (THE UNIVERSITY OF SYDNEY) 2 December 1999. See whole document.	

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report			Patent Family Member	
WO	9961622	AU	40232/99	EP	1082437
WO	9948915	AU	32116/99	EP	1066320

END OF ANNEX